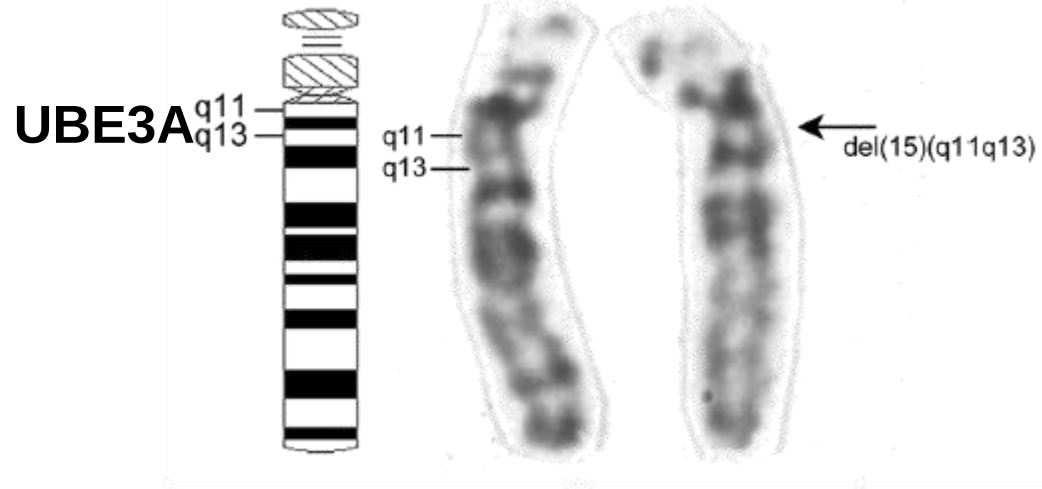


Cognitive deficits in Angelman syndrome - mechanisms and therapy

Hanoch Kaphzan MD PhD MPH

The Lab for Neurobiology of Psychiatric Disorders
Sagol Department of Neurobiology
University of Haifa

Angelman mice model



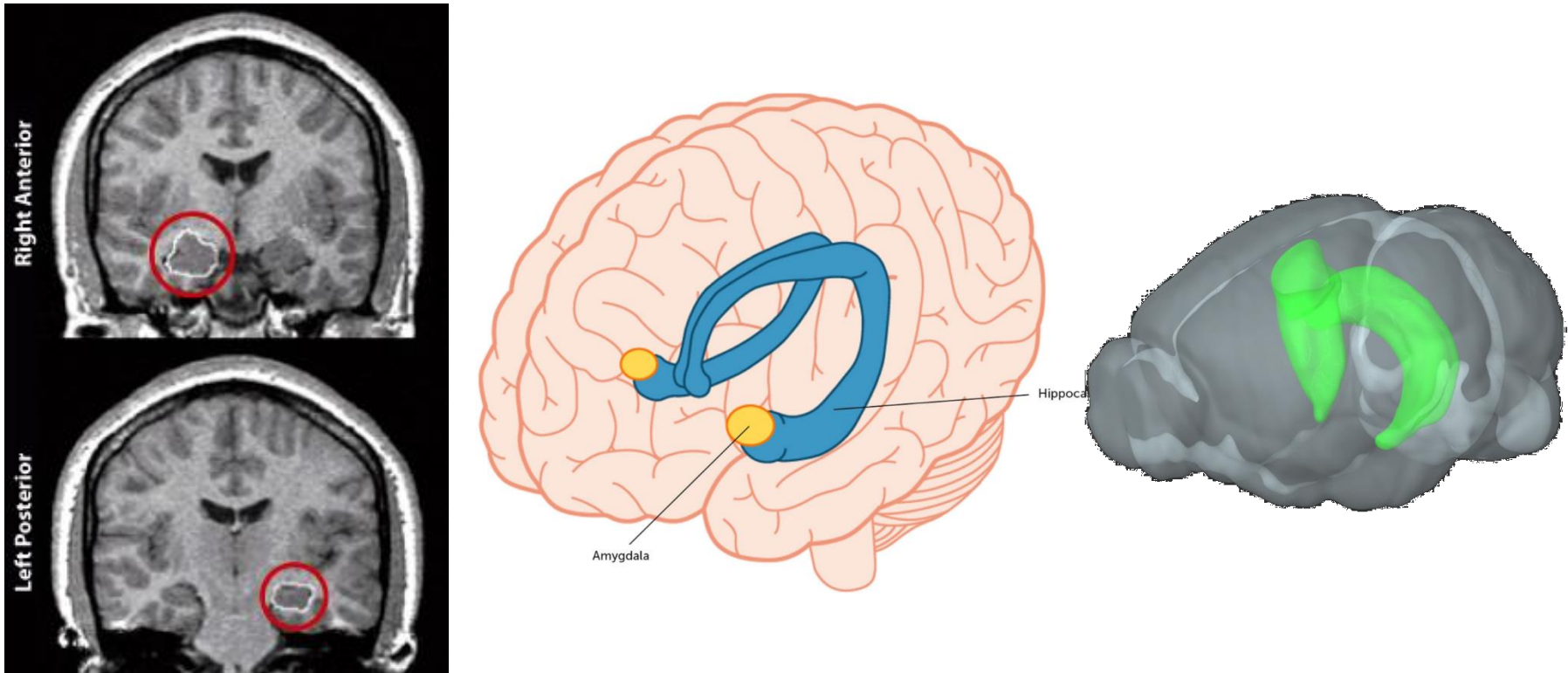
- Kishino et al. (Nat Gen 1997)
Chromosome 15 q11.2-13

- Jiang et al. (Neuron 1998) The first **mice** model.
Mice with **paternal** deficiency (m+/p-) are **similar to wildtype**.
Mice with **maternal** deficiency (m-/p+) resemble human **AS** with motor dysfunction, inducible seizures, a context-dependent learning deficit, impaired social functioning.

- Miura et al. (Neurobiol Dis 2002) A second **mice model** with a different maternal UBE3A gene knock out.
Similar electrophysiological, motor and behavioral phenotype.



**בתסמונת אנגלמן קיימים ליקויים קוגניטיביים.
ליקויים אלה נעוצים בין היתר בתפקוד לקוי של
אזור במוח שנקרא היפוקמפוס.**



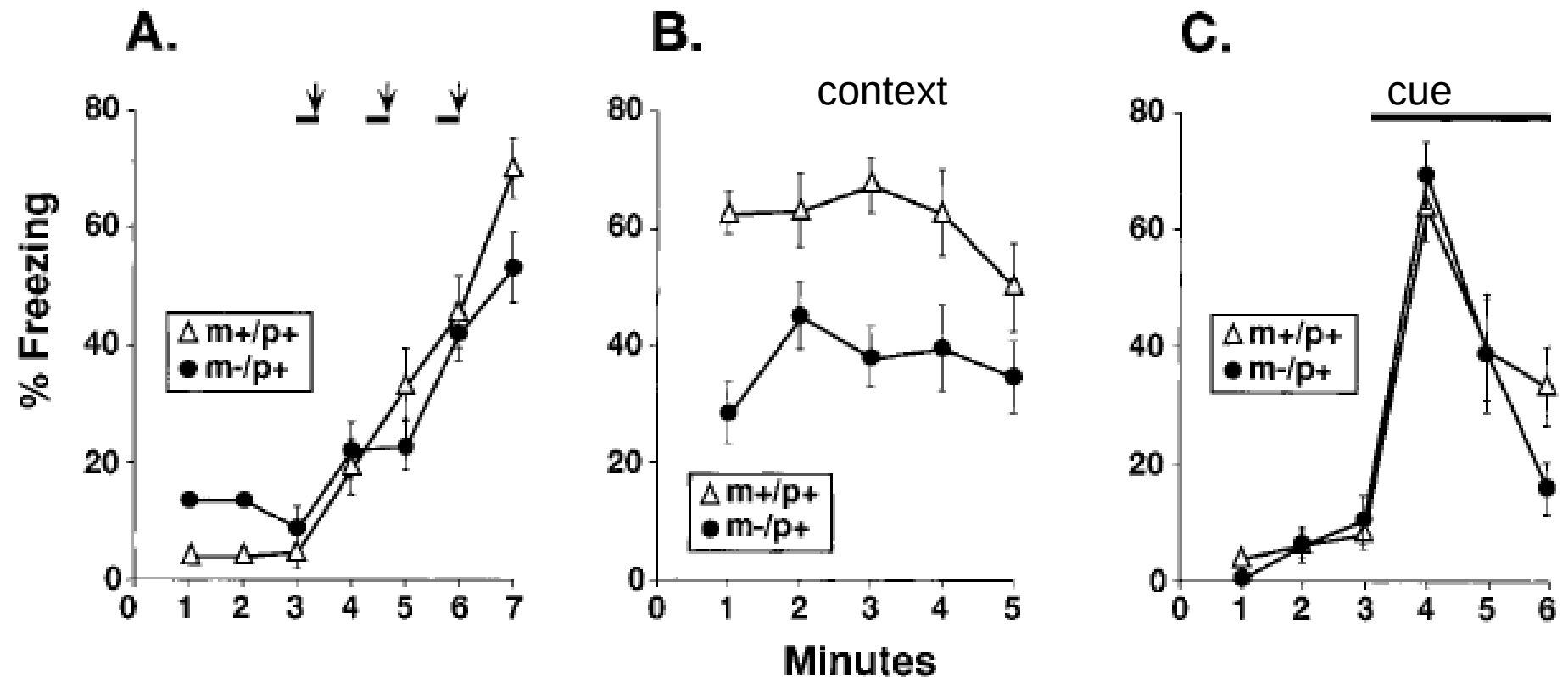
Angelman syndrome entails intellectual disability due to hippocampal deficits

עדות לליקויים בזכרון תלוי היפוקמפוס במודל העכברי לתסמונת אנגלמן

Impaired contextual Fear conditioning

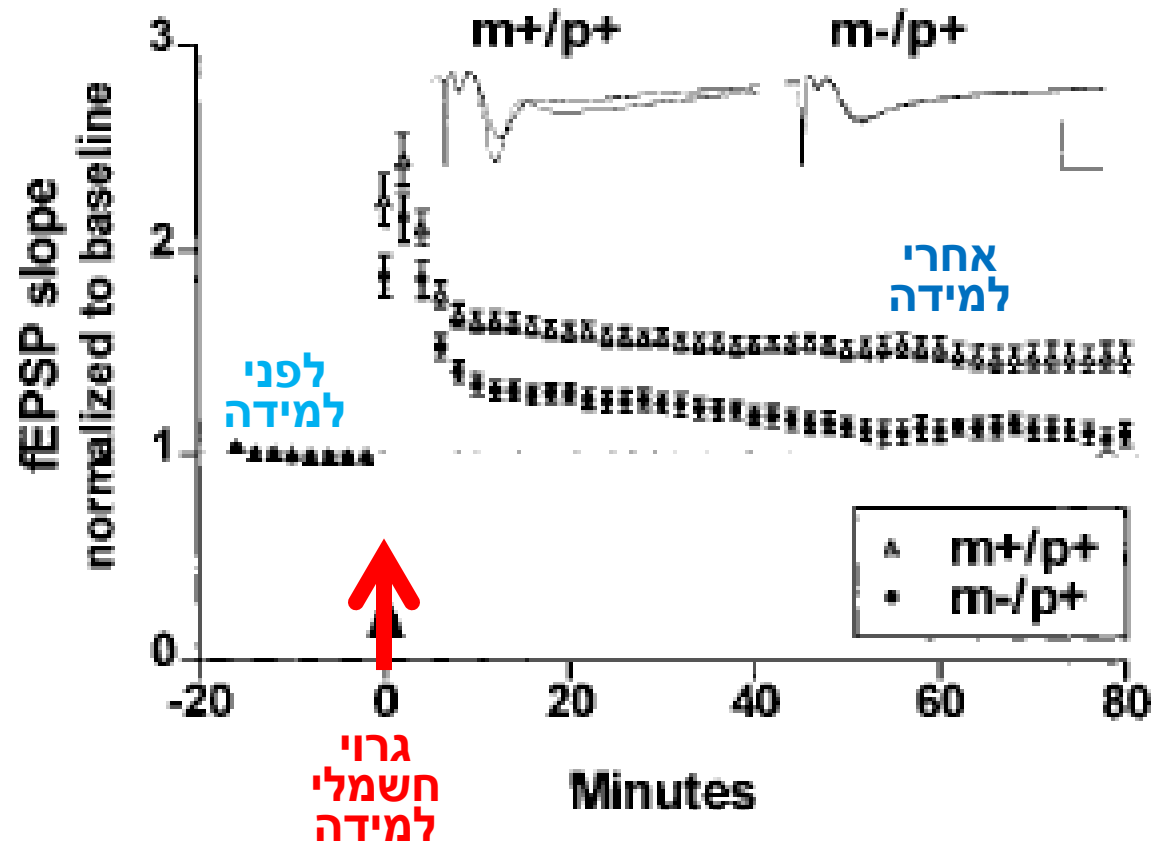
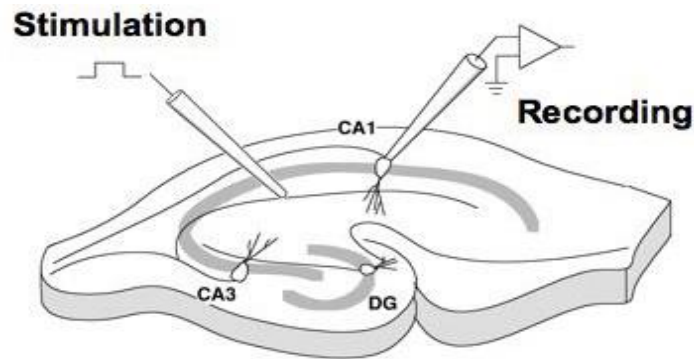
immediate

24h later

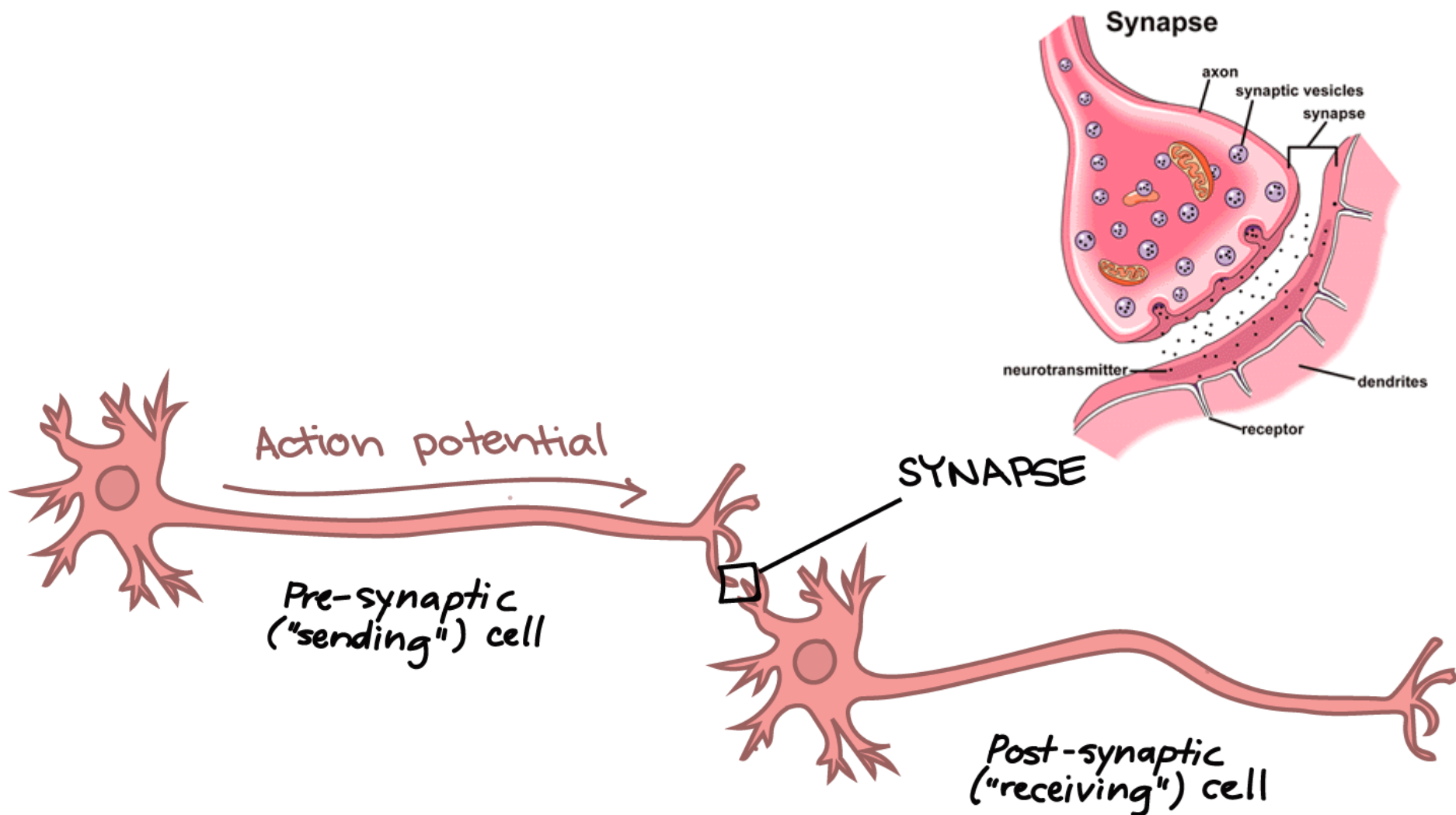


מודל תאי לליקויים בזכרון - במודל עכברי לתסמונת אנגלמן

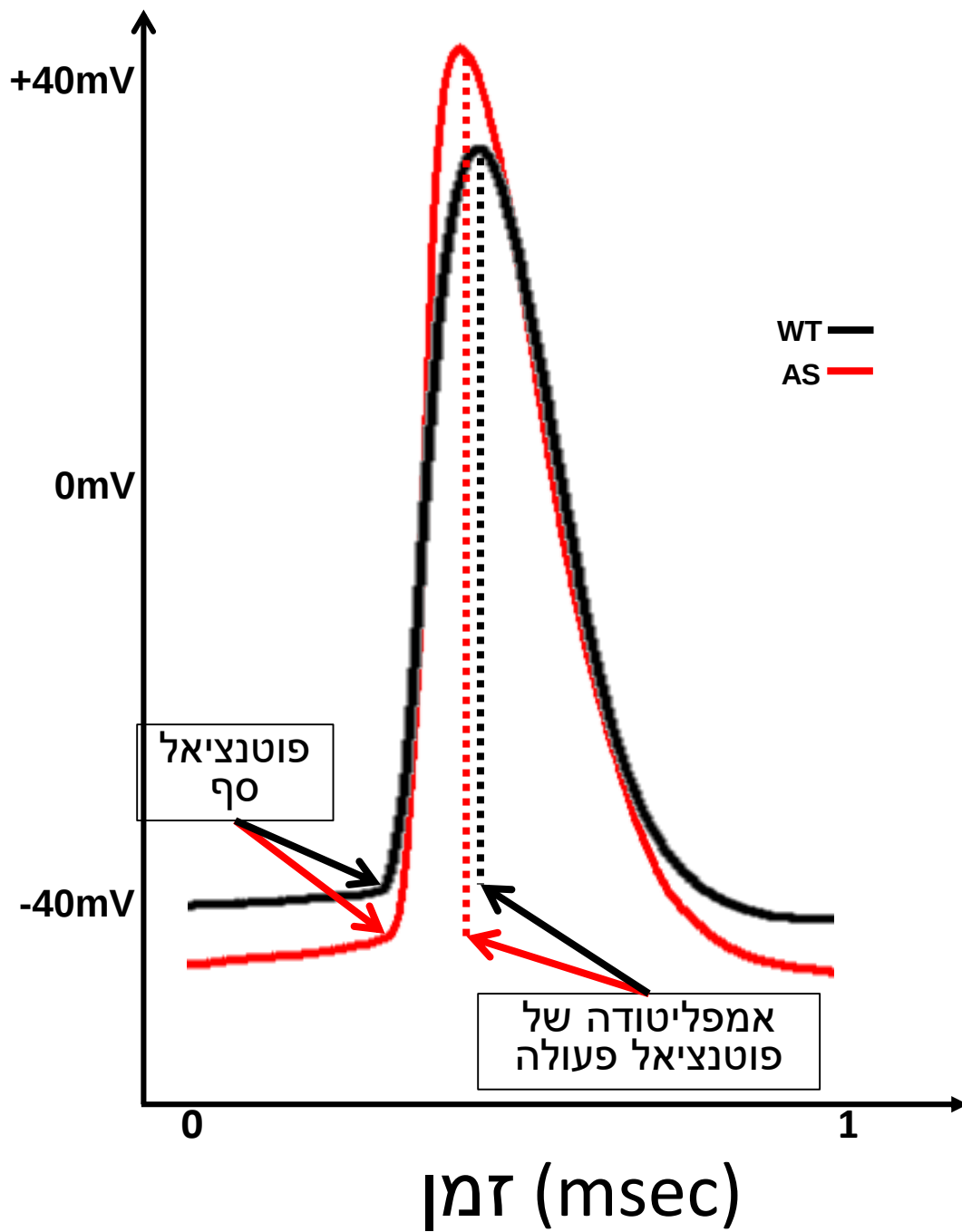
Impaired LTP phenotype



תאי עצב (נוירונים) והקשרים ביניהם

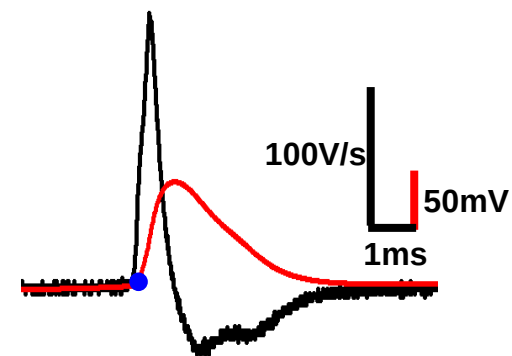
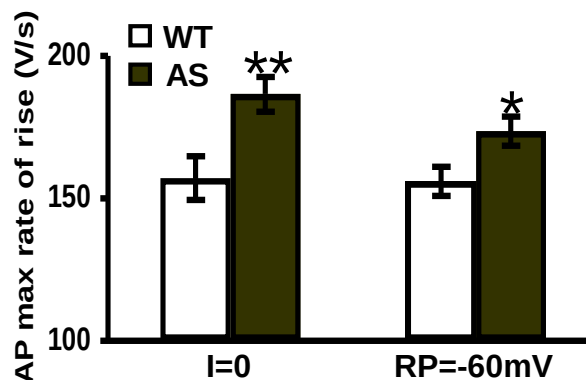
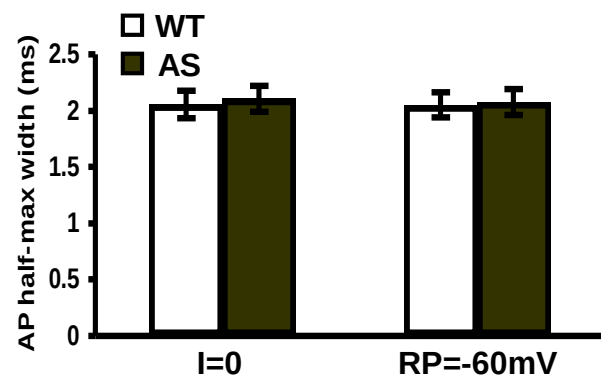
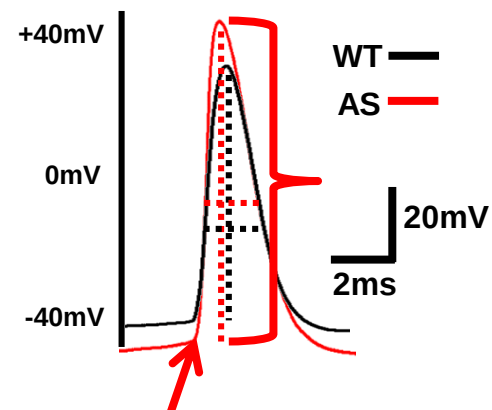
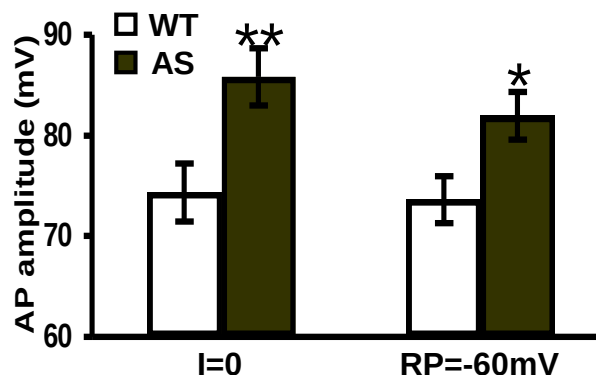
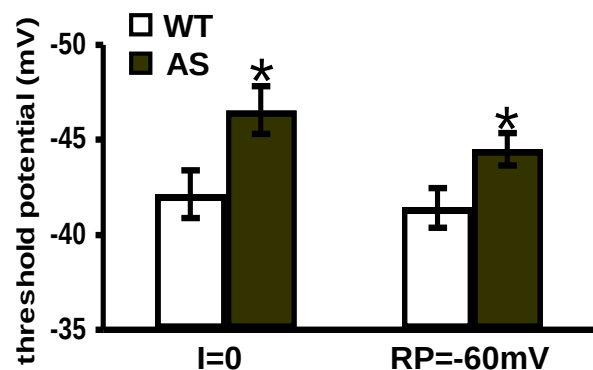


מתח חשמלי של קרום התא

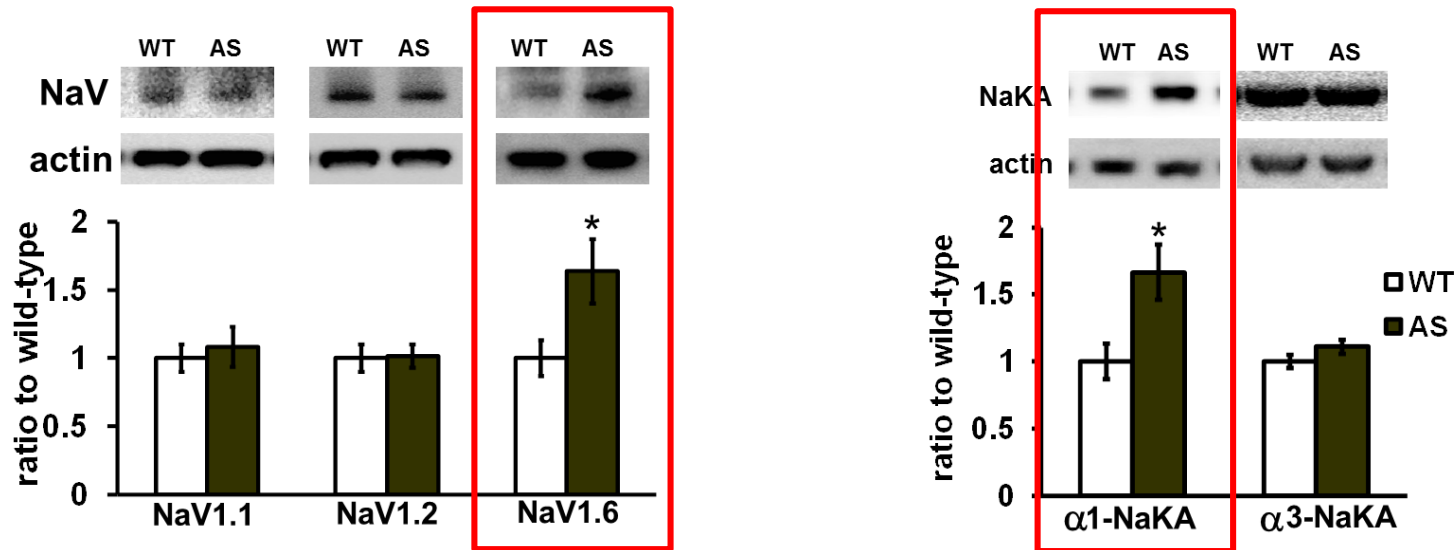


CA1 pyramidal cells intrinsic membrane properties

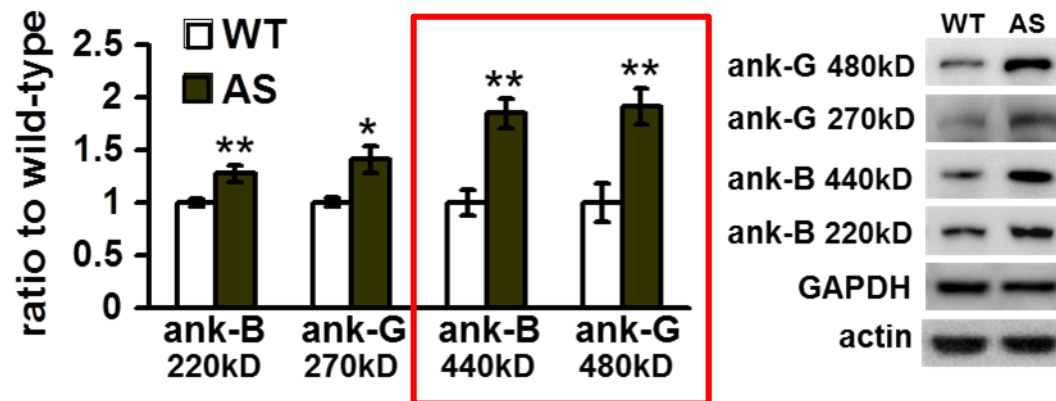
parameter	WT	AS	p-value
Resting potential (mV)	-61.7 (± 1.5)	-66.4 (± 1.5)	<0.05
Time constant	29.2 (1.9)	29.0 (2.0)	ns
Input resistance (M Ω)	237.8 (13.2)	239.8 (13.1)	ns



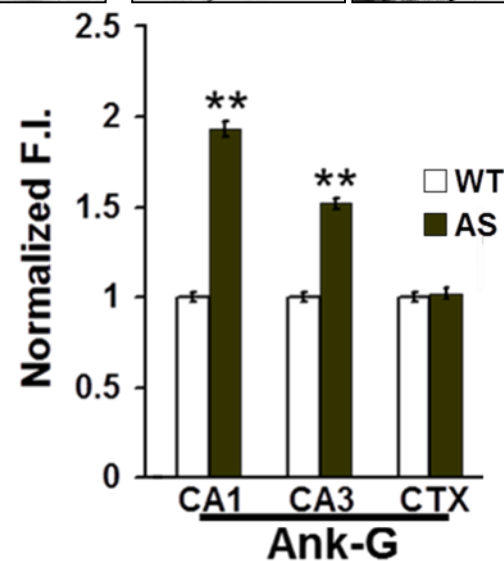
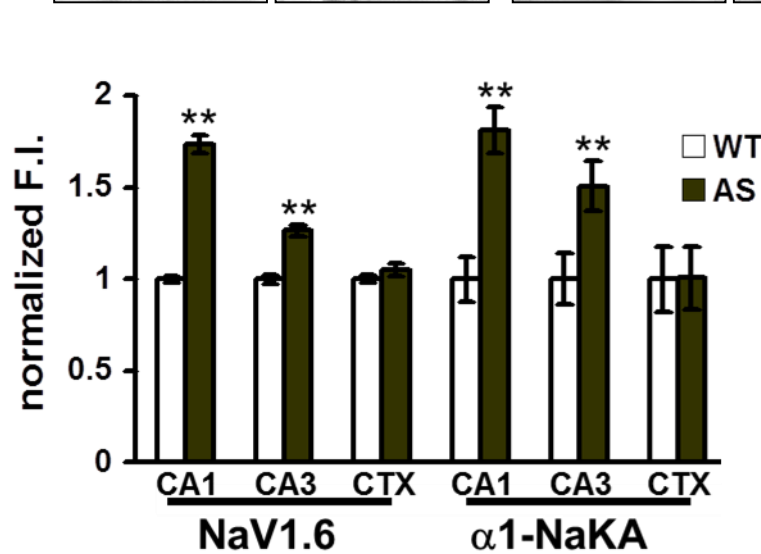
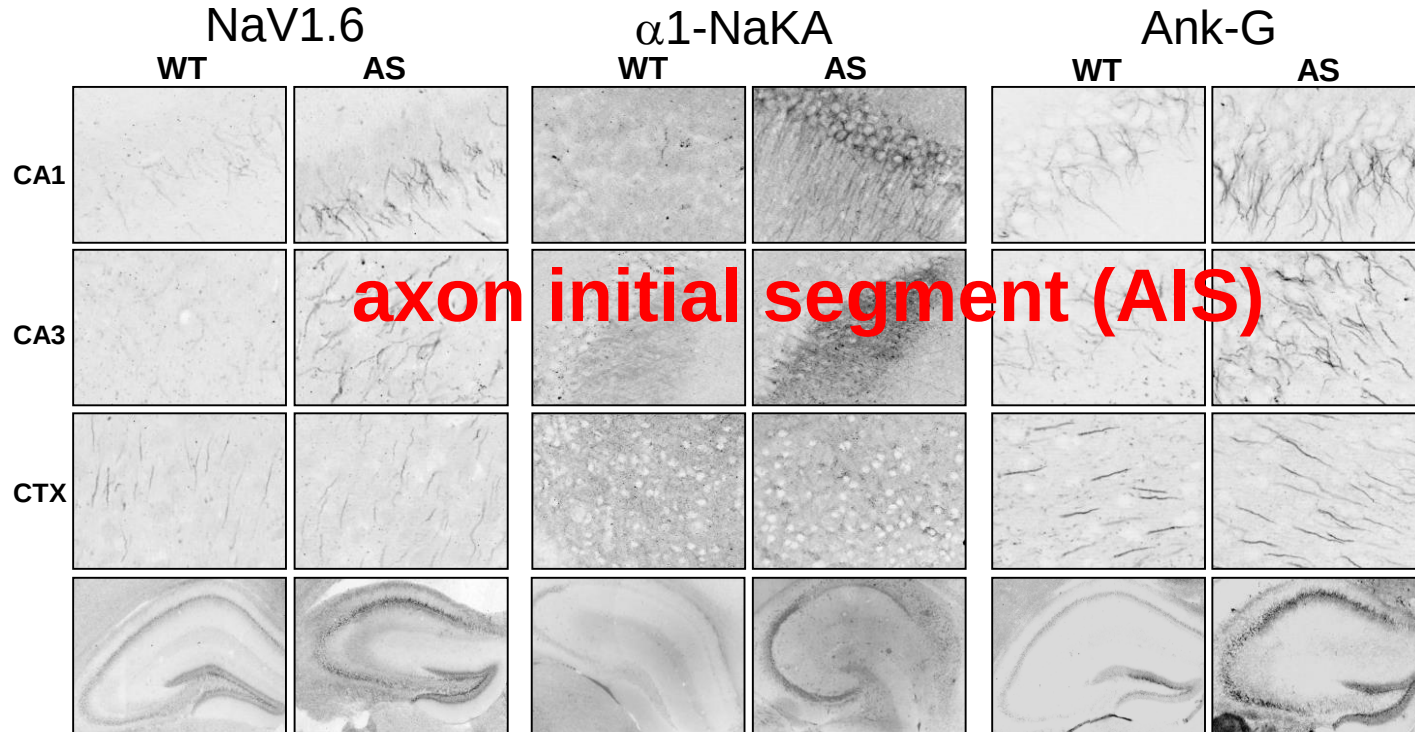
NaV1.6 sodium channels and $\alpha 1$ -Na/K-ATPase pump expression in the hippocampus is increased



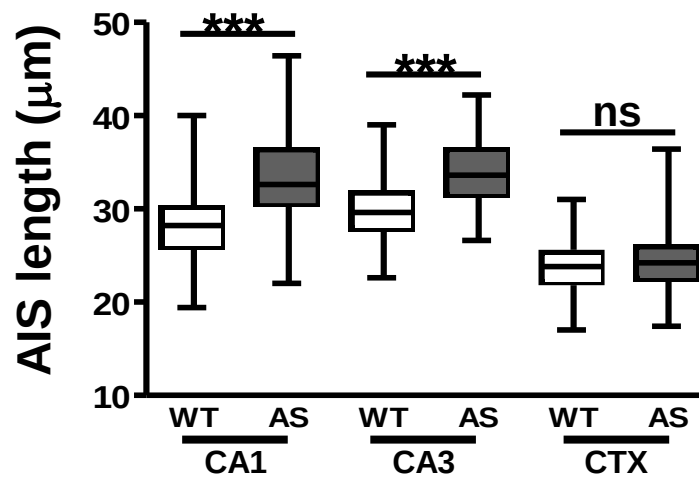
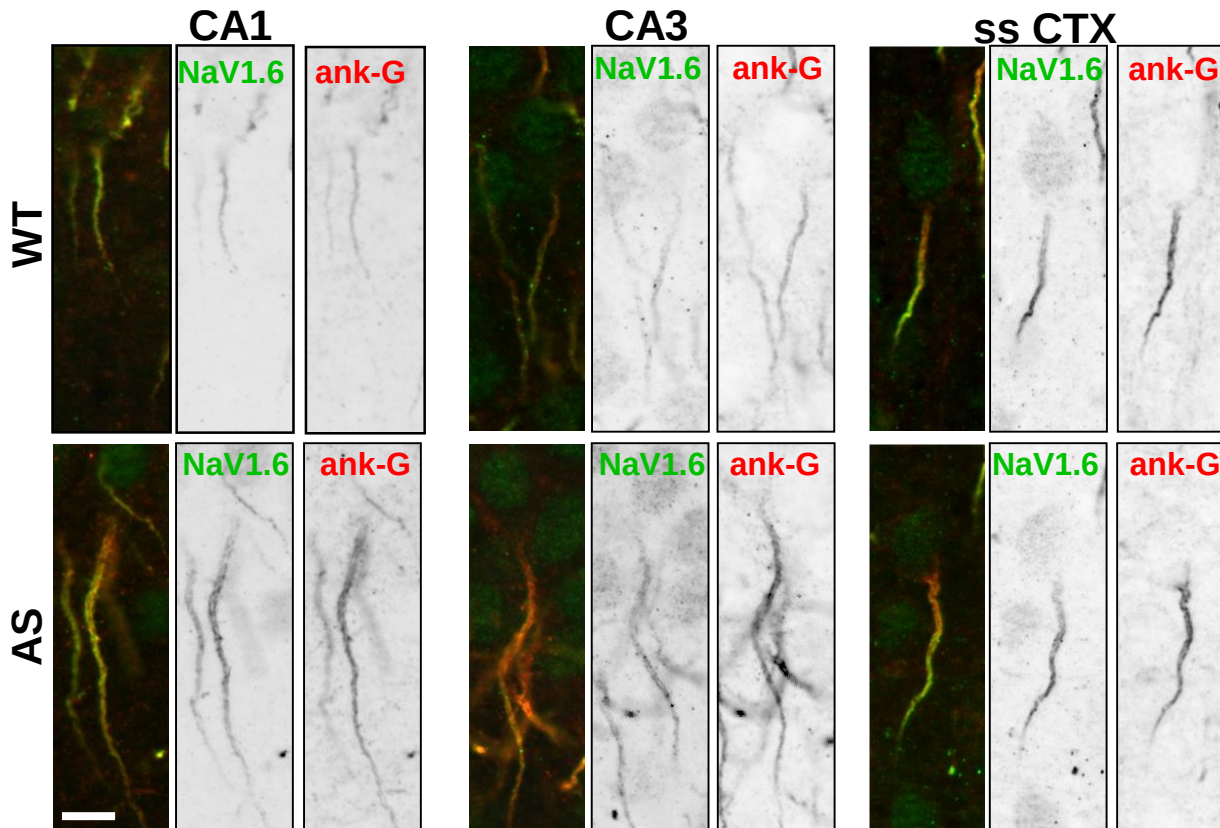
proteins that interact with NaV1.6 and $\alpha 1$ -NaKA are increased



Expression of NaV1.6, $\alpha 1$ -NaKA and ankG in hippocampal subregions

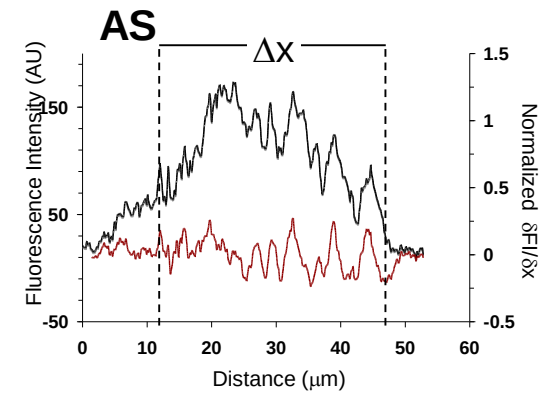
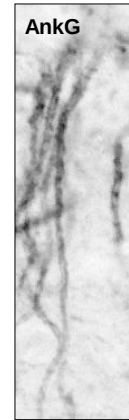
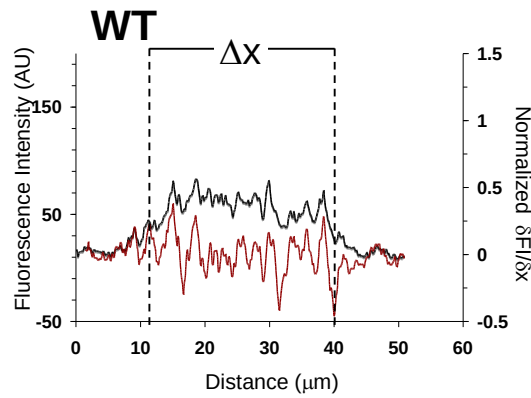
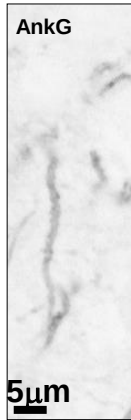


AIS in the AS mice is longer

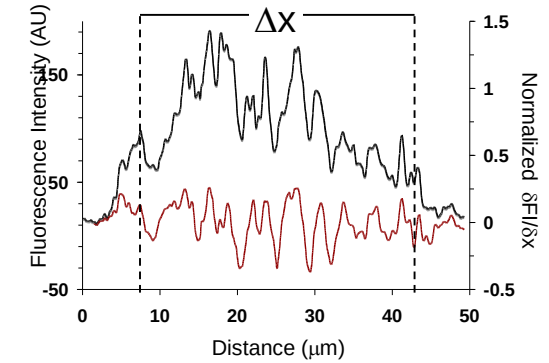
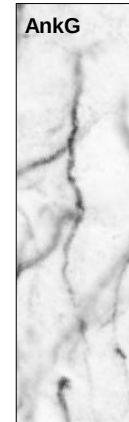
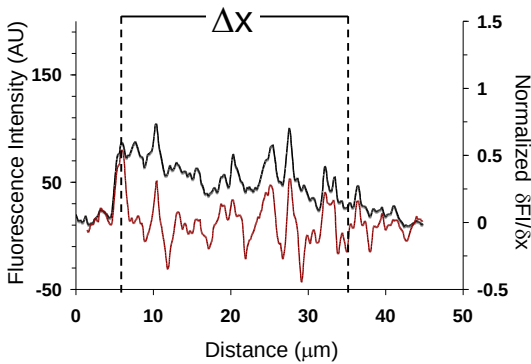


AIS Channels density of the in AS mice is increased

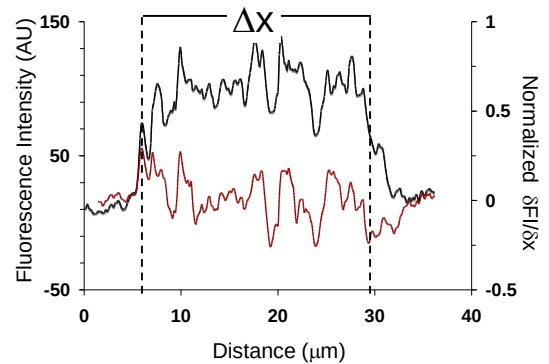
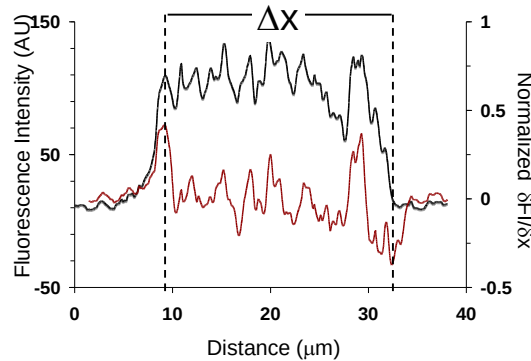
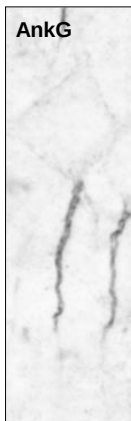
Hippocampal CA1



Hippocampal CA3



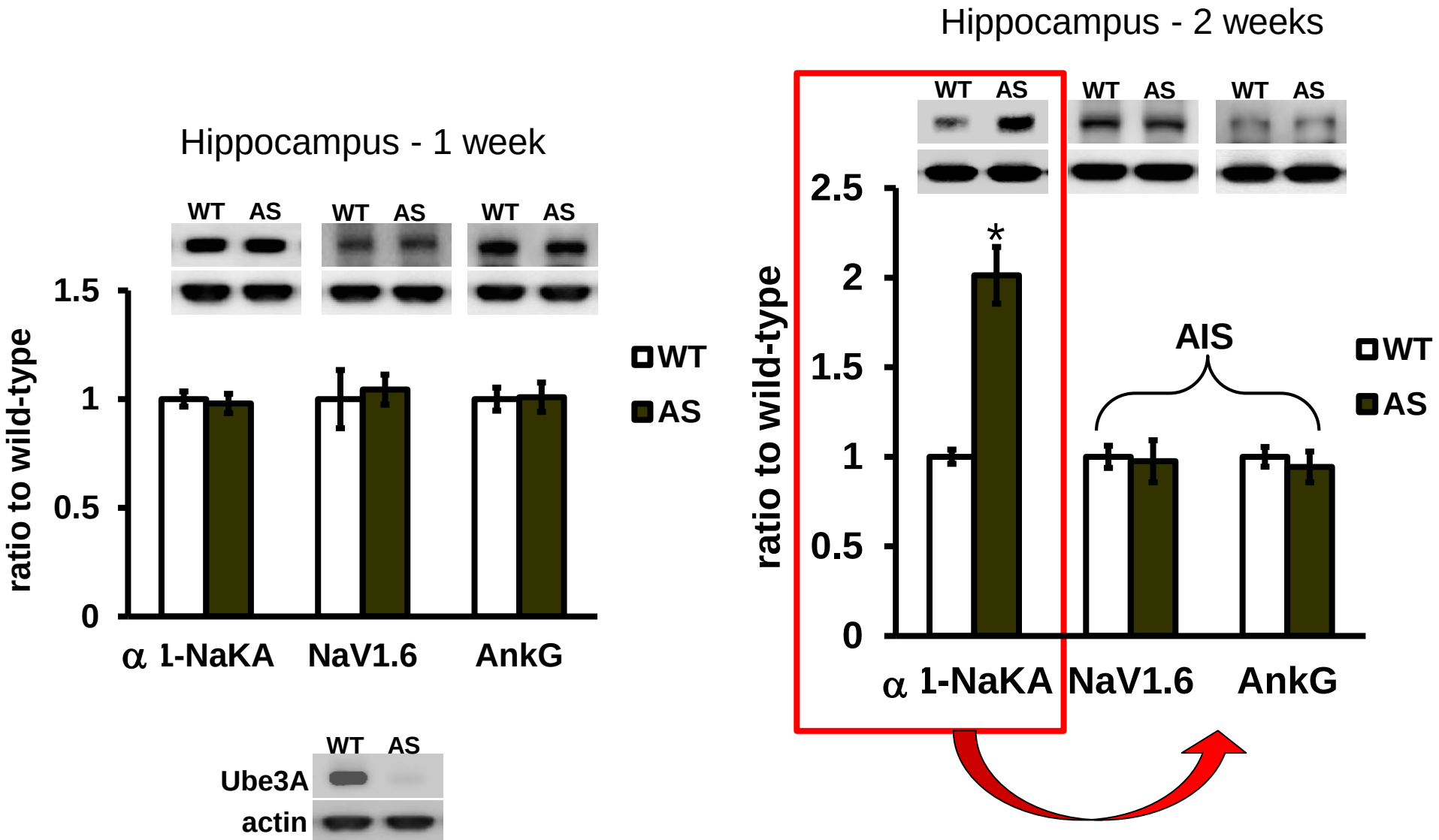
Somatosensory Cortex



— Fluorescence Intensity (FI) vs. Distance (x) — $\delta\text{FI}/\delta x$

מתי השינויים מופיעים לאורך ההתפתחות?

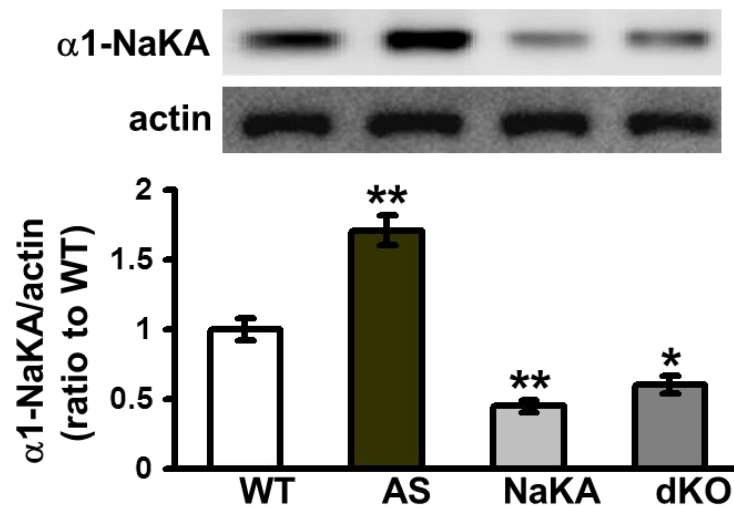
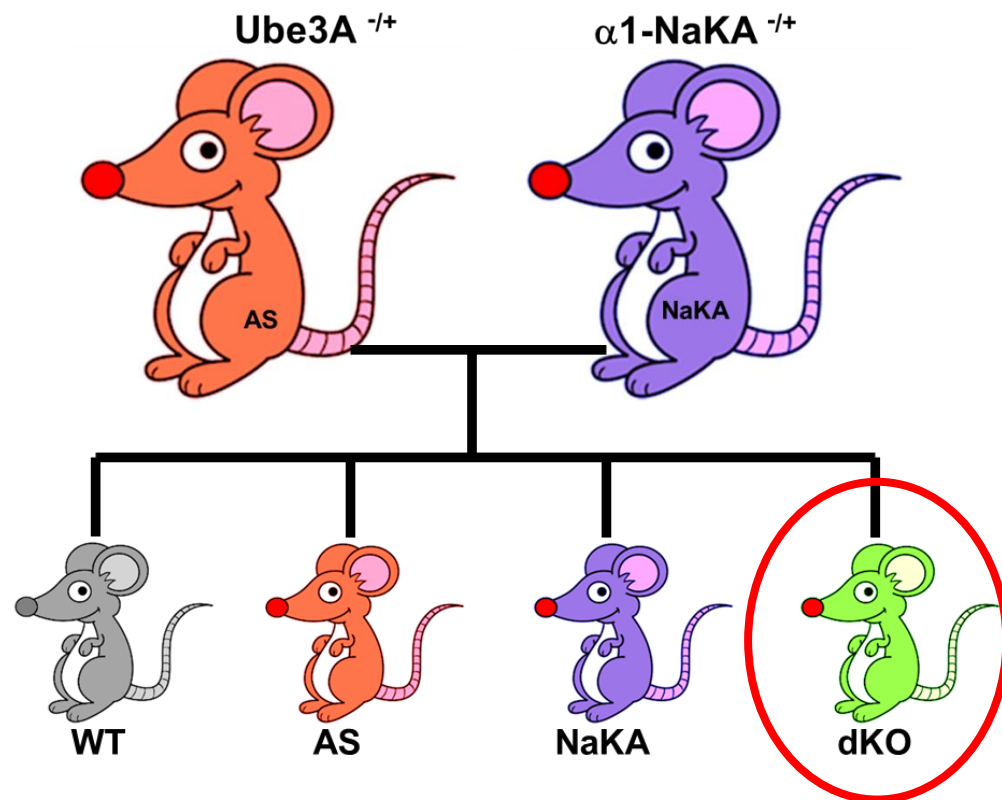
Proteins expression during development

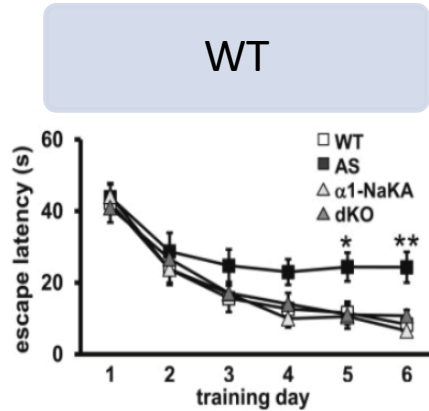
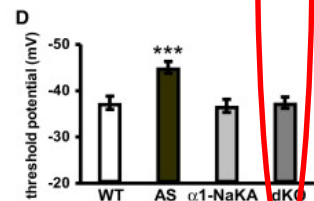
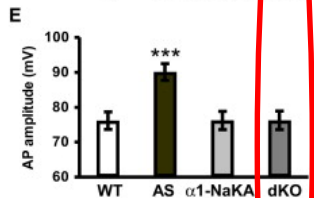
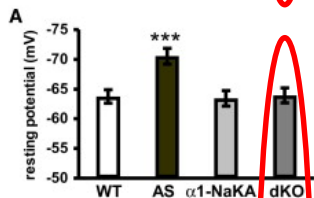
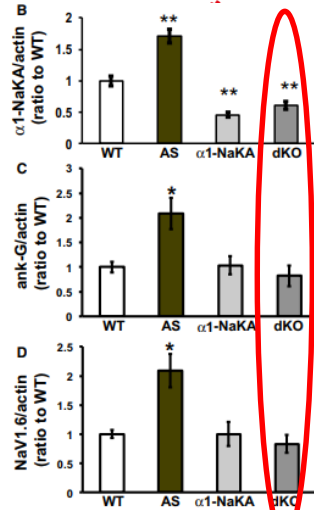


~~$\alpha 1$ -NaKA $\uparrow$~~

Excitability $\downarrow$

AIS length $\uparrow$





Normal $\alpha 1\text{-NaKA}$,
AnK-G and NaV1.6
expression levels

Normal intrinsic
membrane properties

Normal hippocampal
memory

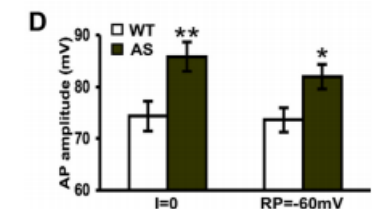
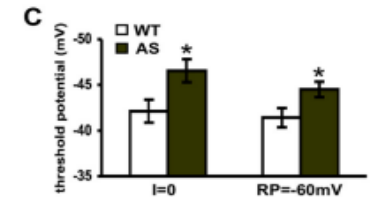
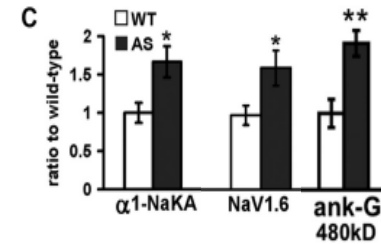
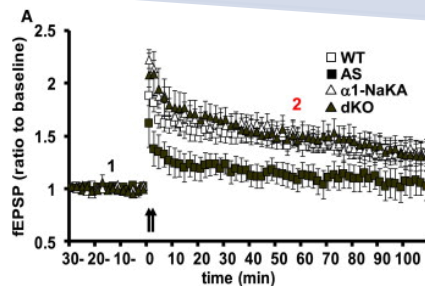
AS

$\Delta \alpha 1\text{-NaKA}$ levels

Δ Ankyrin-G (ankG)
and Δ NaV1.6

Altered Intrinsic
membrane properties

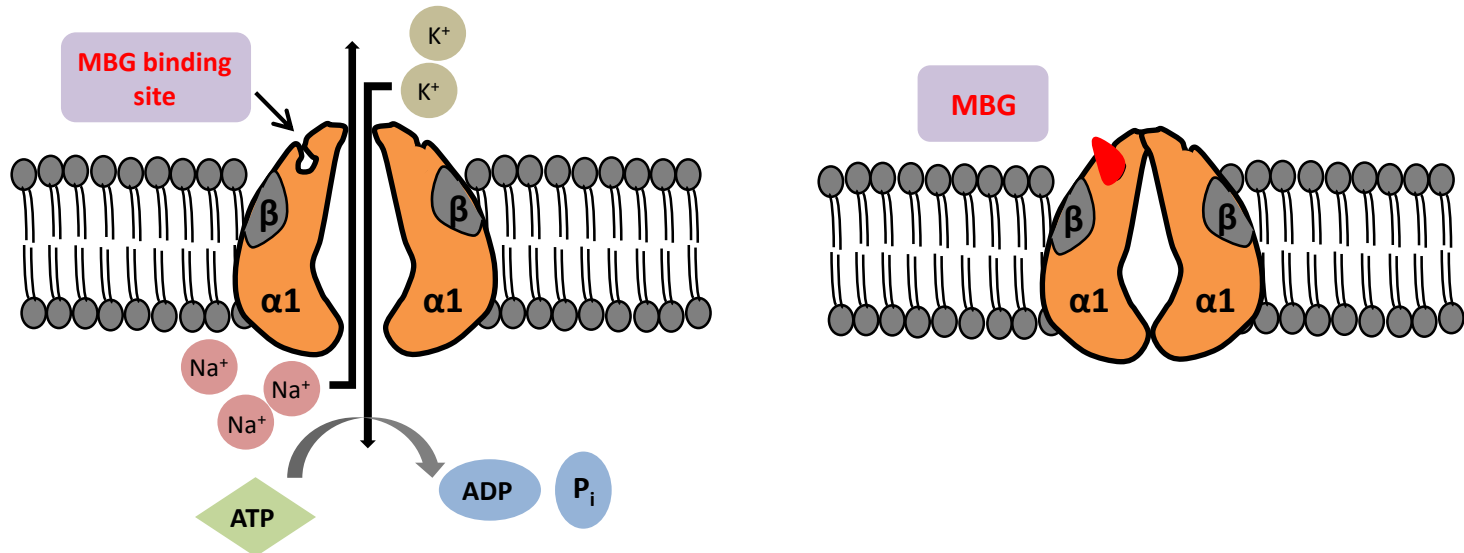
Impaired hippocampal
memory

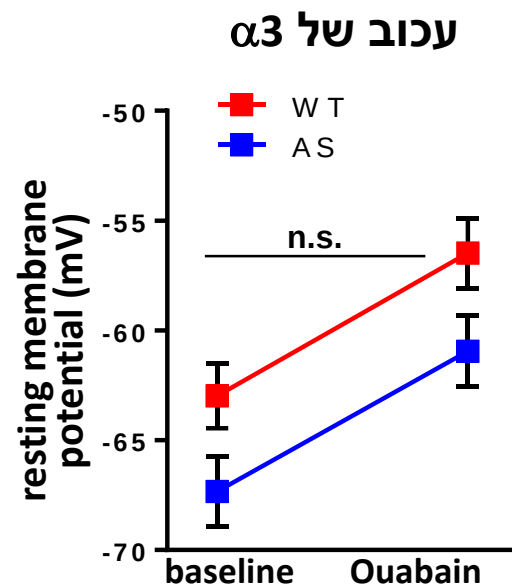
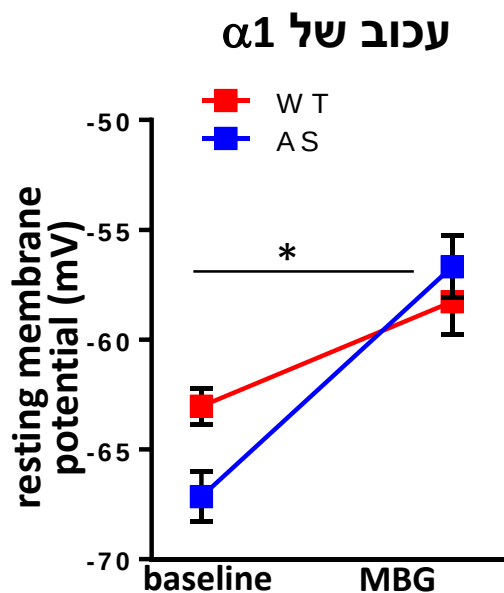


האם ניתן להשתמש בתרופה שתעכב את משאבת נתרן-אשלגן?

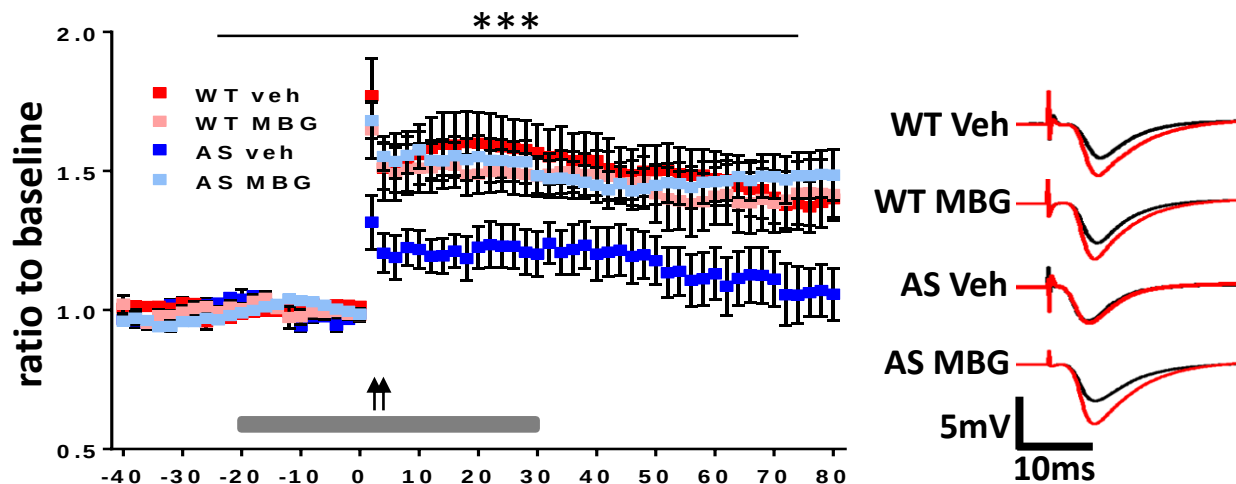
Na/K-ATPase

- The sodium pump, or Na/K-ATPase is a house keeping gene that catalyzes the active transport of cations across the cell membrane by utilizing ATP.
- A vital transporter which maintains the cellular resting membrane potential.
- Marinobufagenin (MBG) is a bufadienolide that selectively inhibits $\alpha 1$ -NaKA (Fedorova and Bagrov 1997).



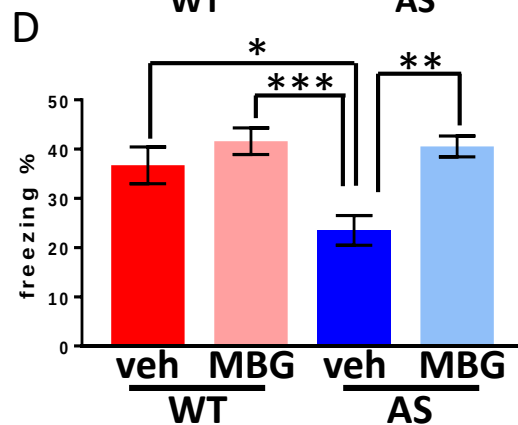
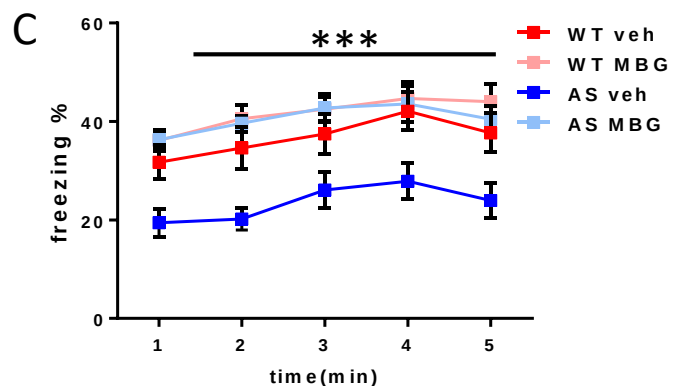
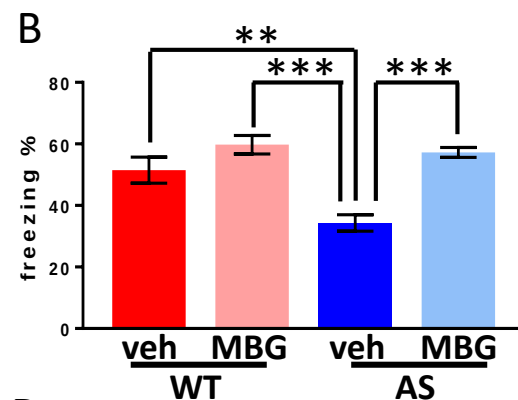
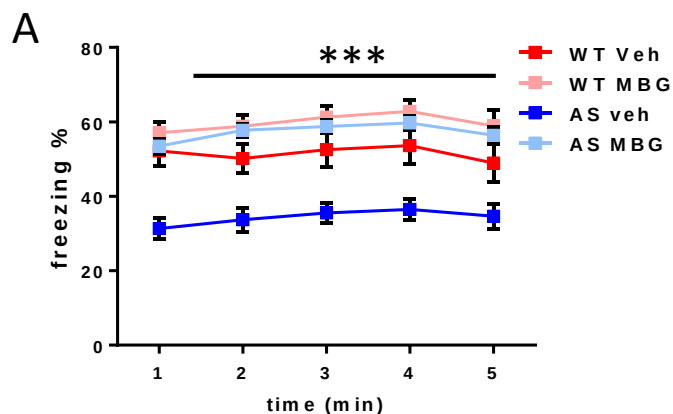


מעכב משאבת נתרן אשלגן משפר זכרון תאי של נוירונים בהיפוקמפוס



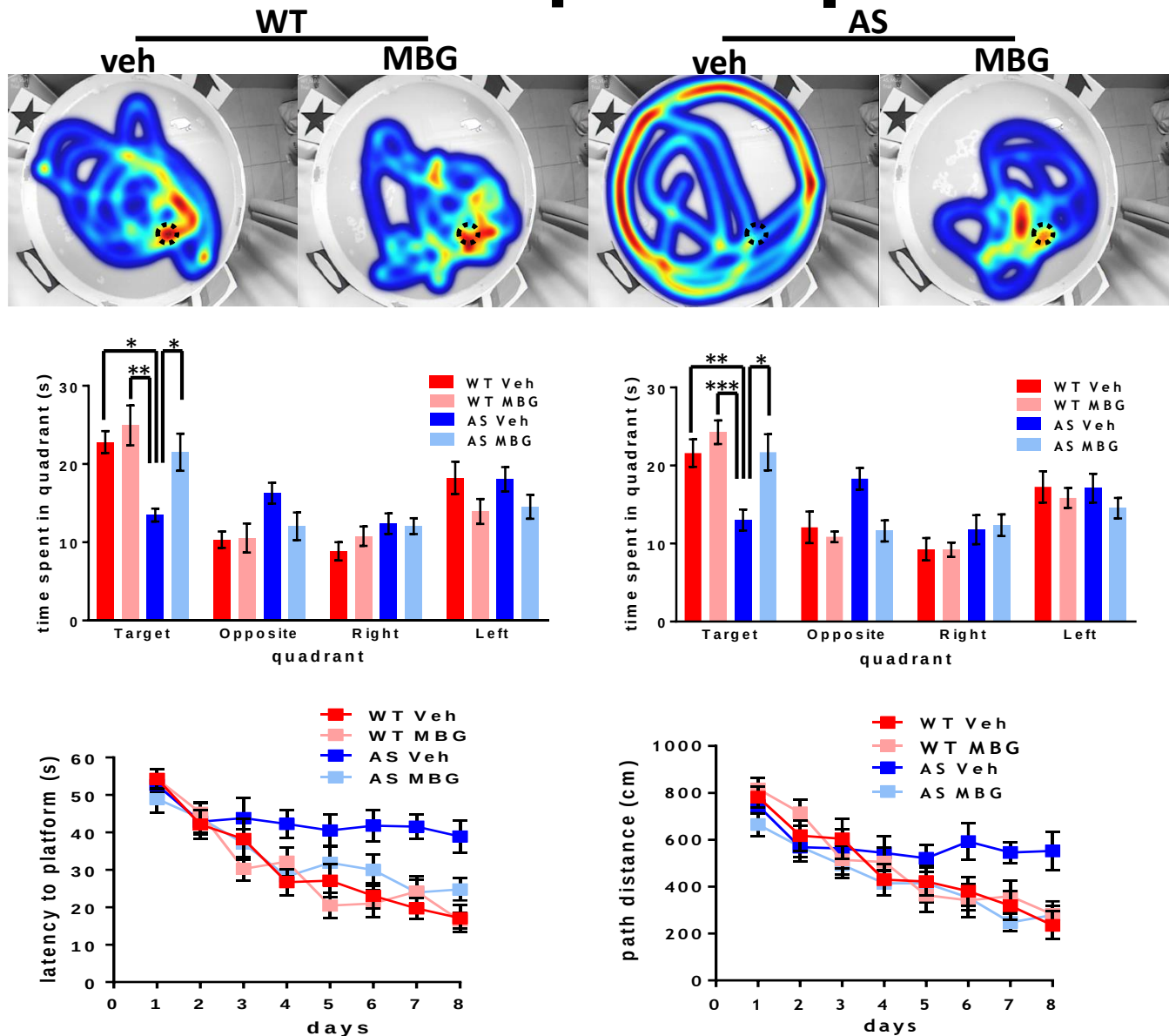
זכרון תלוי היפוקמפוס

זכרון של פחד מקונטקסט ספציפי

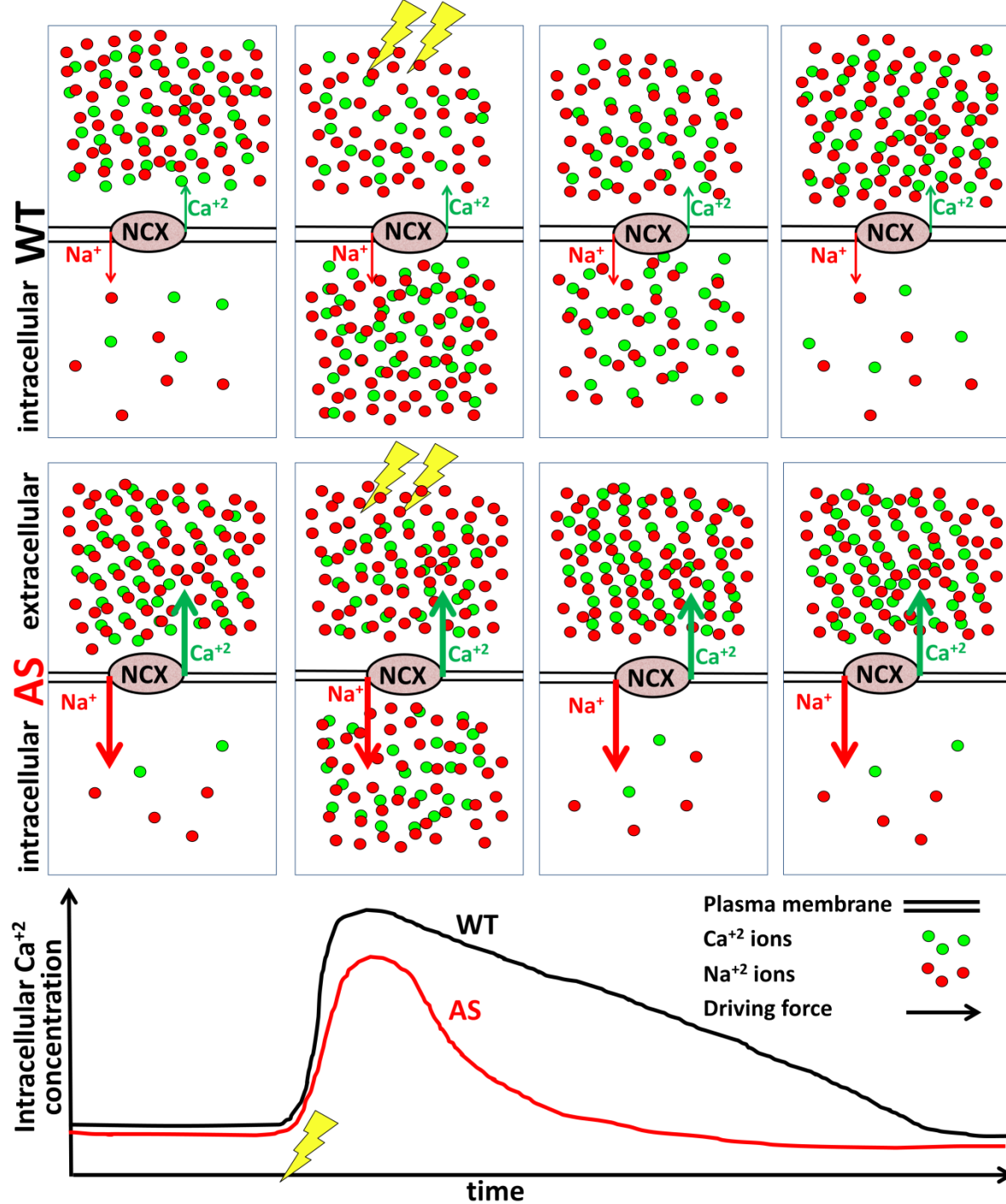
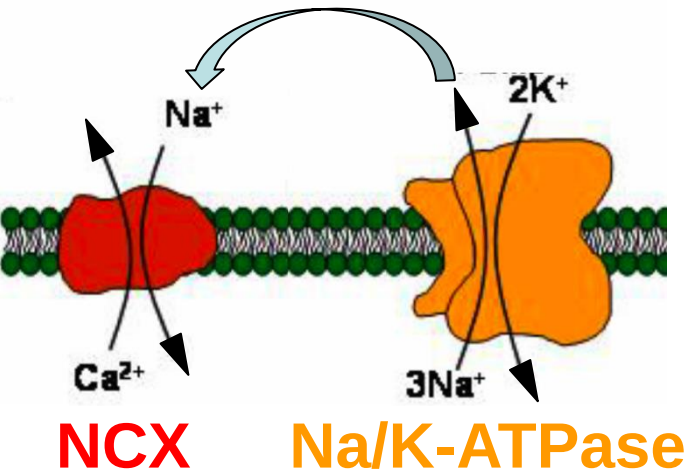


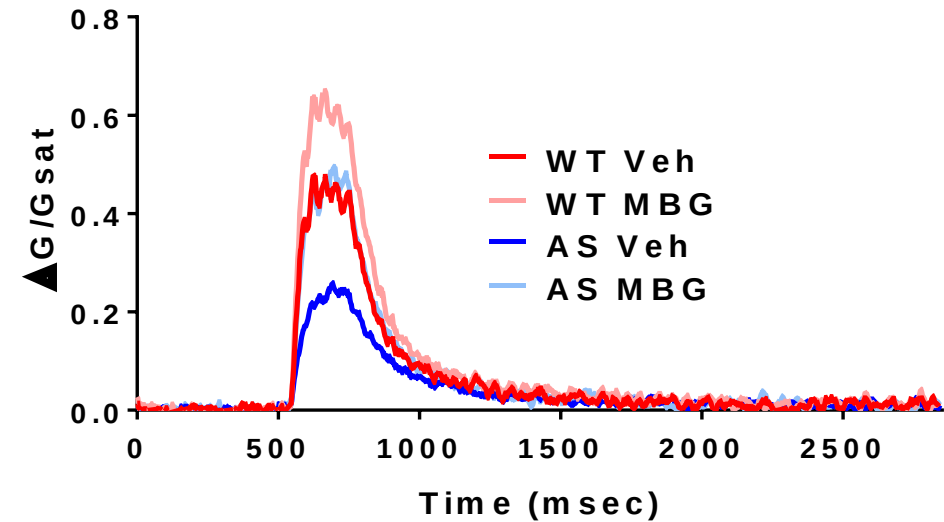
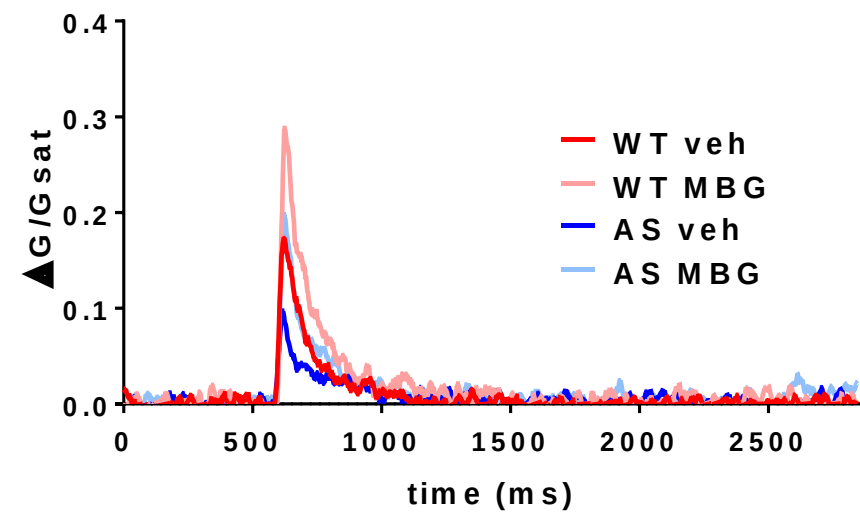
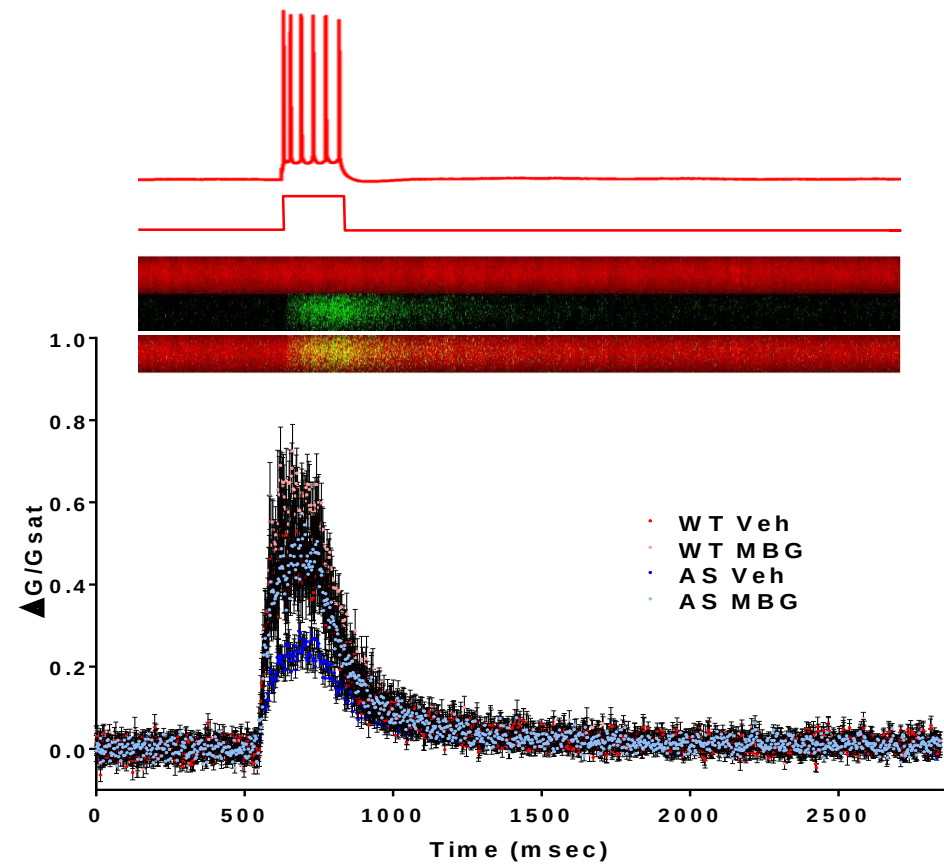
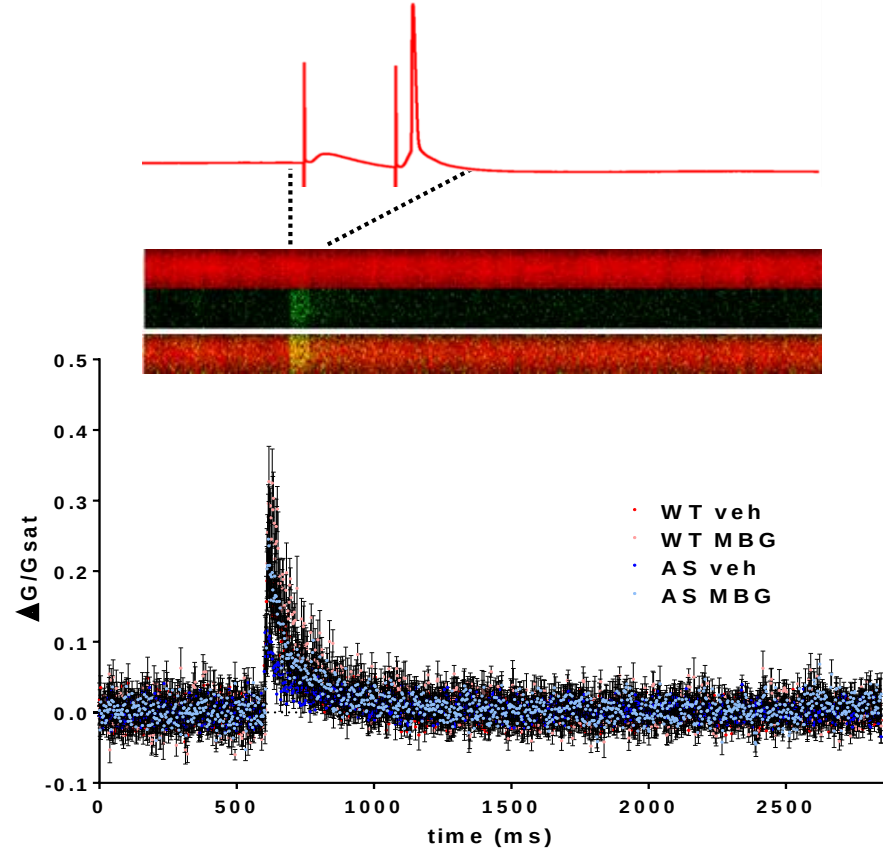
זכרון תלוי היפוקמפוס – מבוך מים ע"ש מוריס

זכרון של מיקום ויכולת נווט

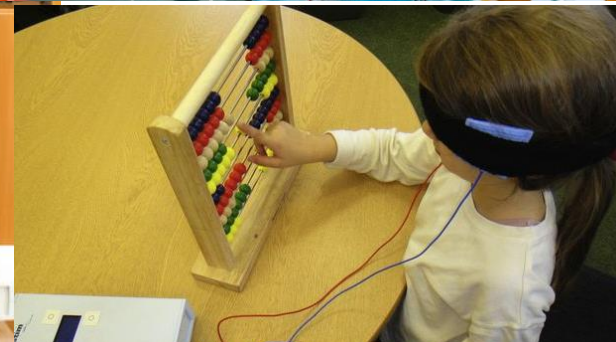


Calcium hypothesis for hippocampal AS deficits

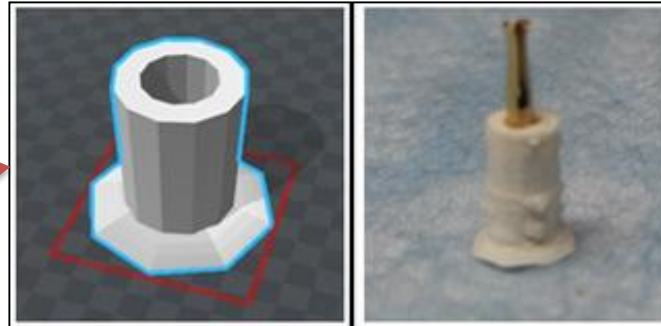
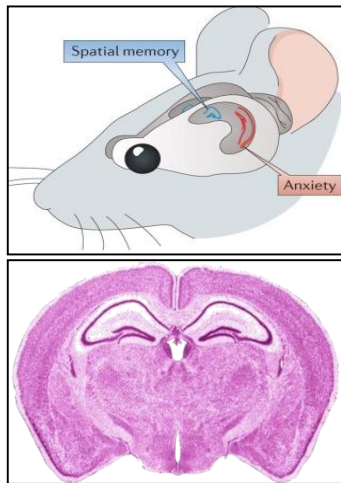




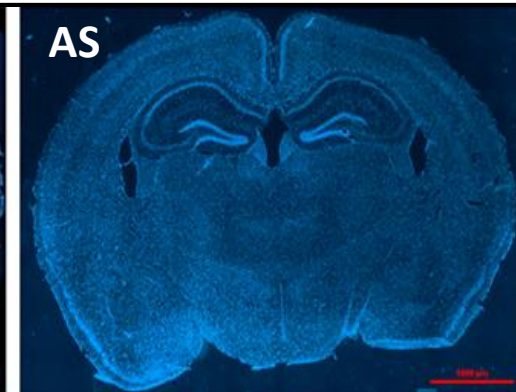
Transcranial Direct Current Stimulation (tDCS)



גריה חשמלית לא פולשנית ע"י transcranial direct current stimulation (tDCS) בתסמונת אנגלמן

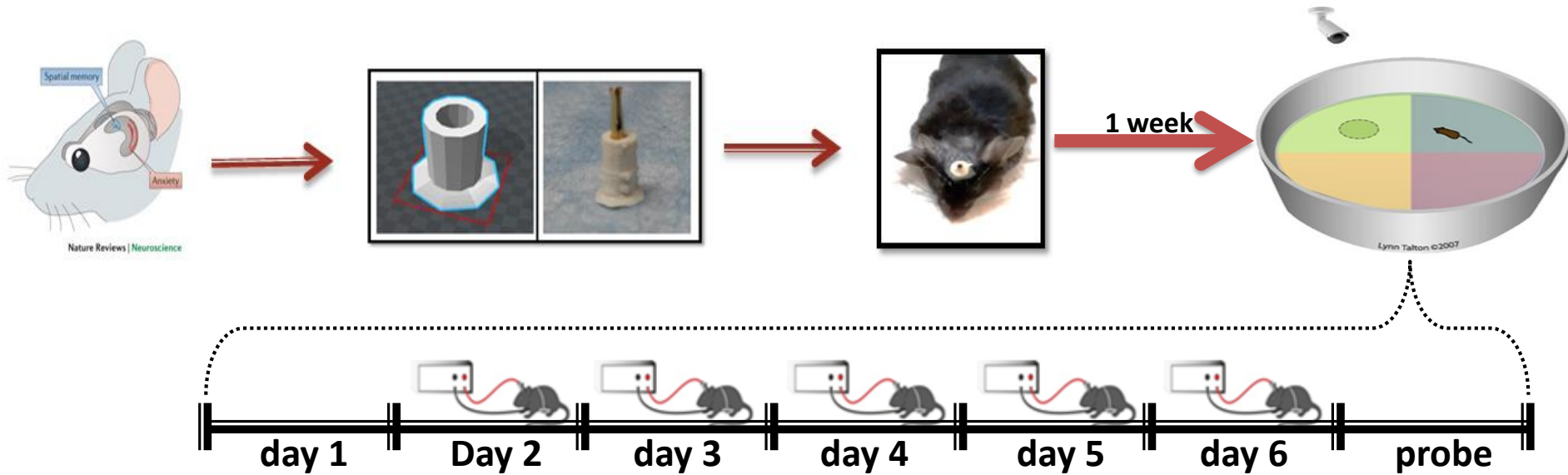


$150\mu\text{A}$
 $\sim 31\mu\text{A}/\text{mm}^2$



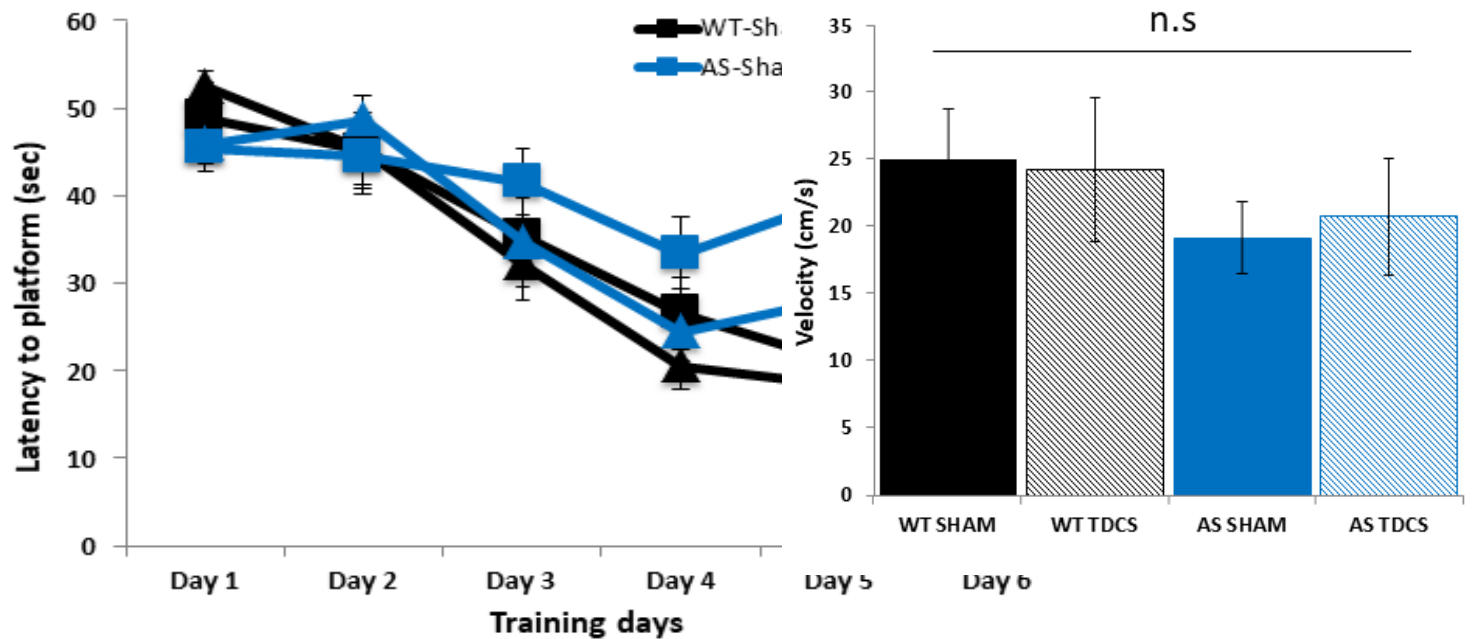
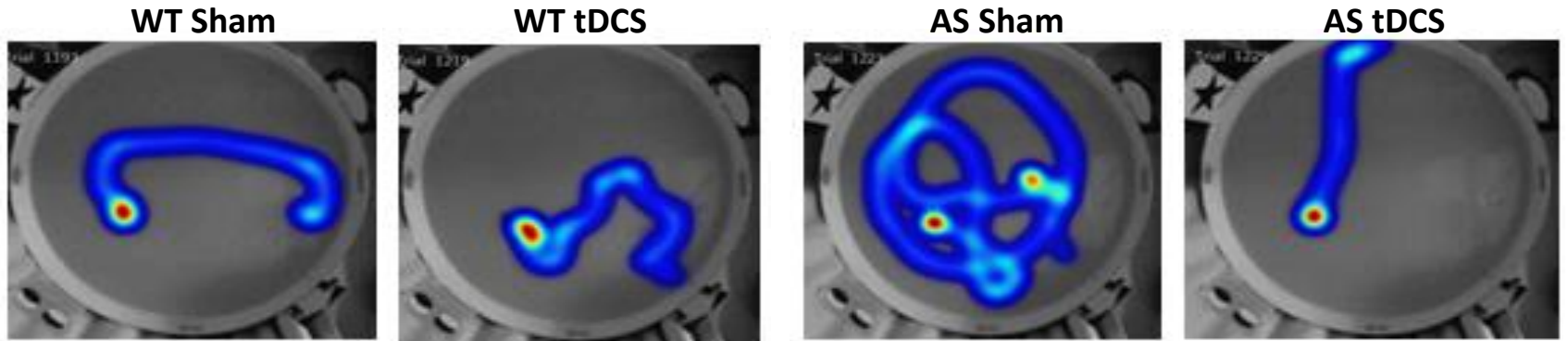
זכרון תלוי היפוקמפוס – זכרון למיקום ונווט

Morris water maze

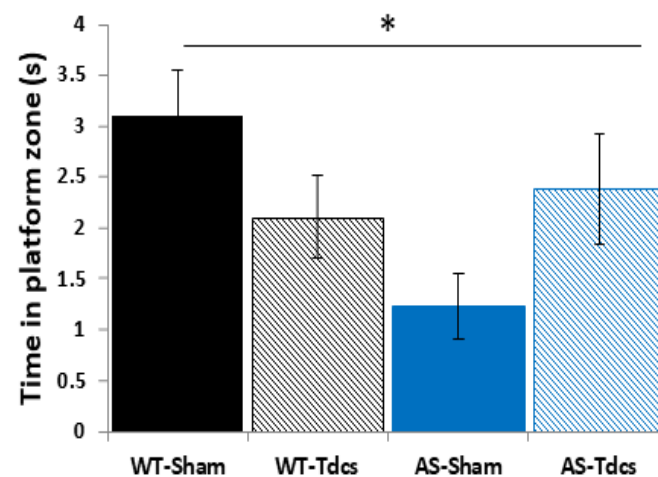
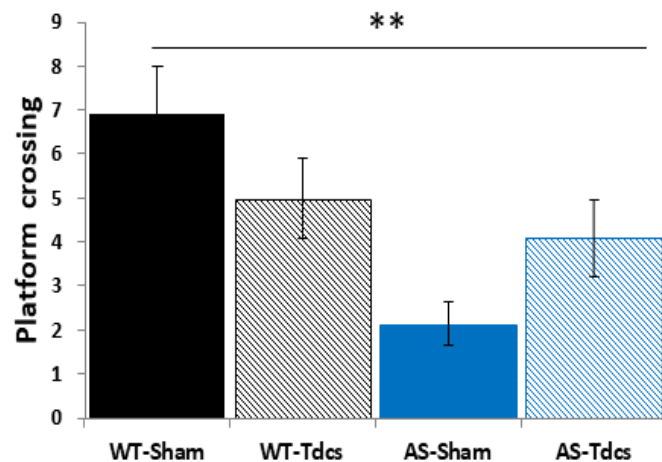
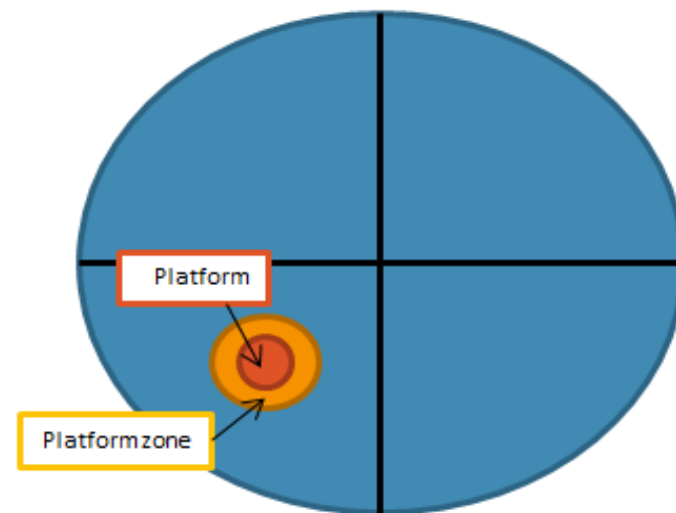
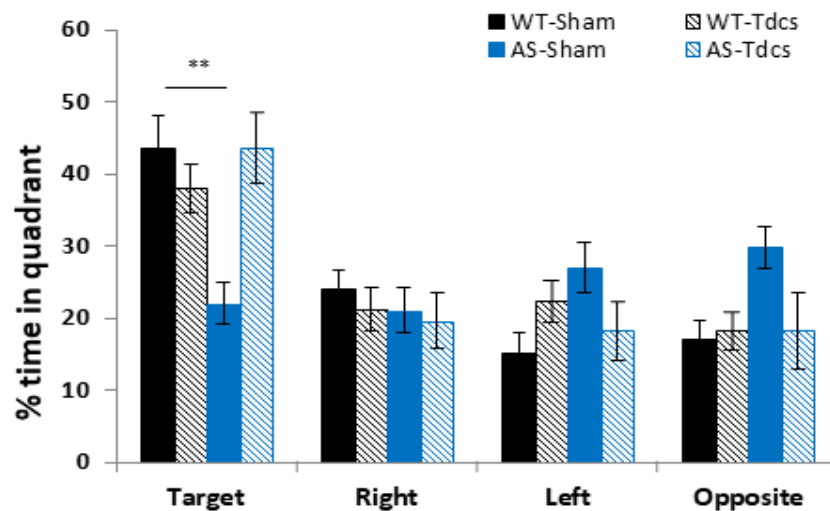


Anodic Stimulation: $150\mu\text{A}$ * 20 min
~1min before training

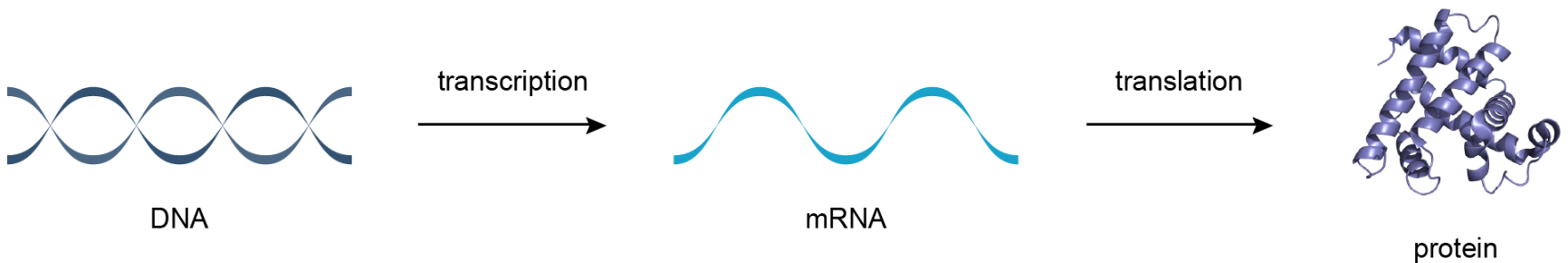
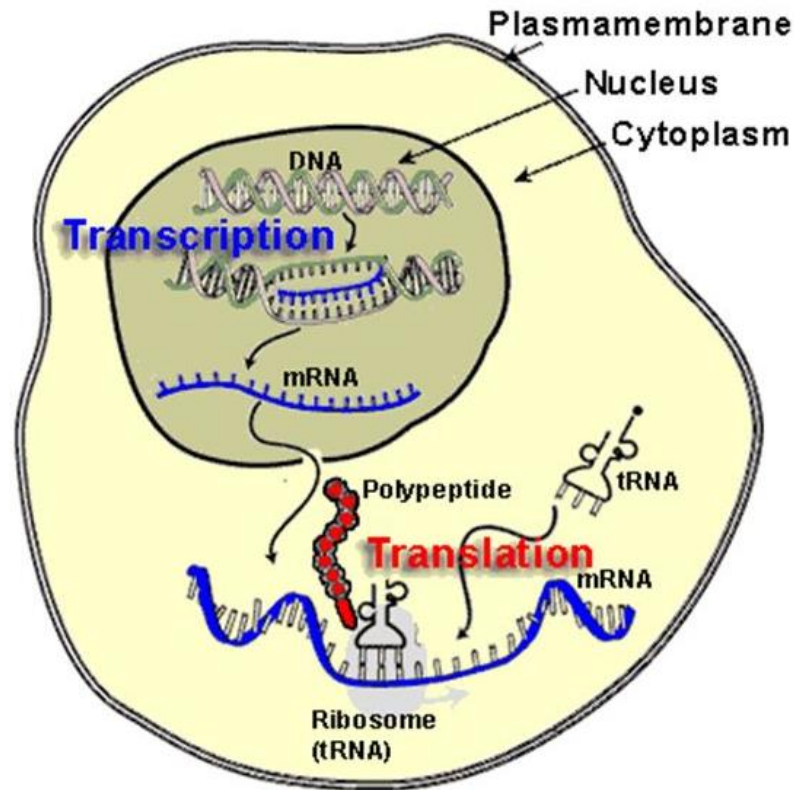
תוצאות של מבוך מים ע"ש מוריס

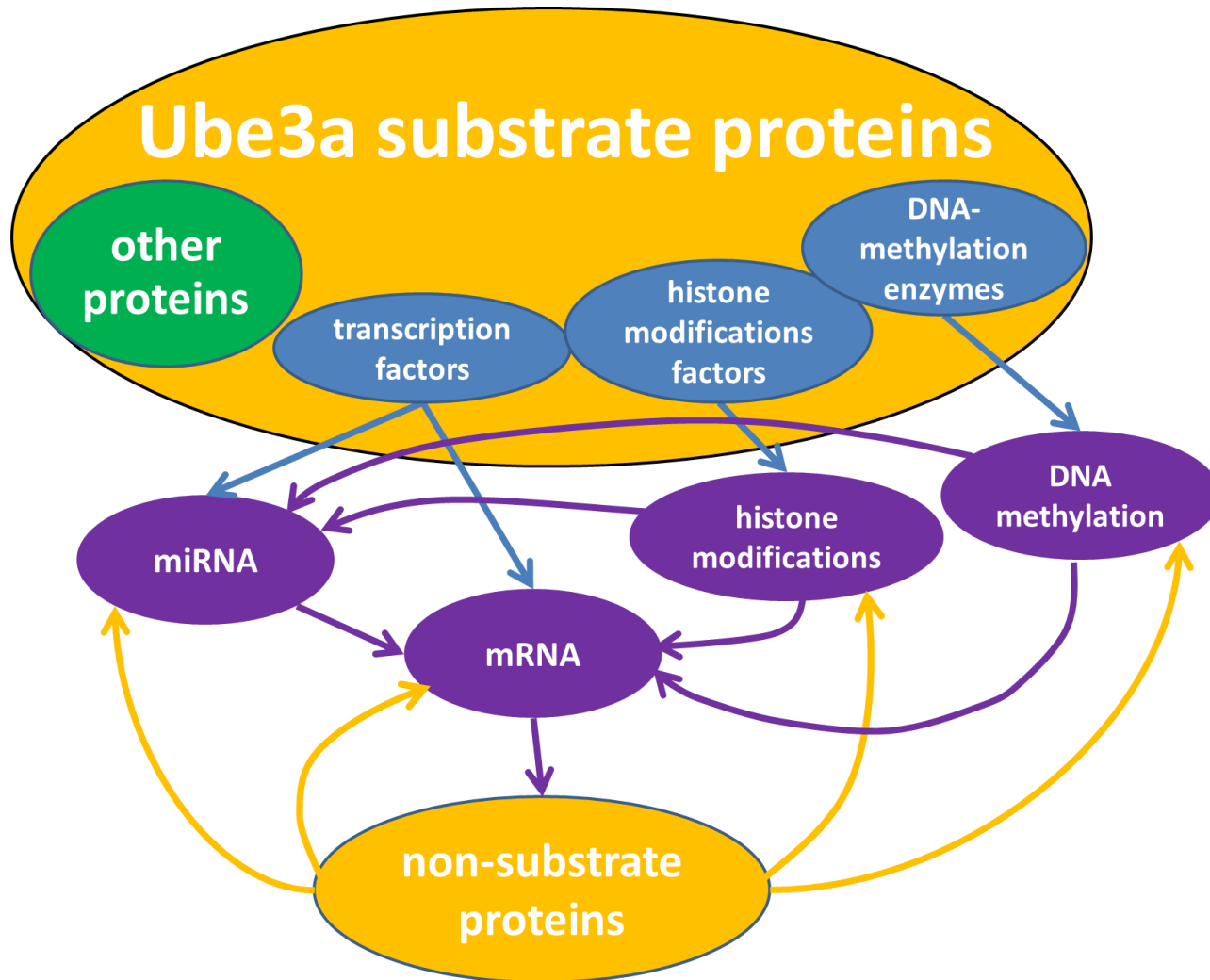


תוצאות של מבחן מים ע"ש מוריס (המשך)



אינטראקציות והשפעות מולקולריות דינמיות של חלבון Ube3A





THANK YOU !

Lab members

Yonatan Feuerman PhD

Prudhvi Raj Rayi

Olga Lopatkin

Sreerag Othayoth Vasu

Lilach Simchi

Julia Panov

Ola Mursi

Lab alumni

Darpan Chakraborty

Lee Koyavski

